EXHIBIT C

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
AT CHARLESTON

IN RE: ETHICON, INC. PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION	Master File No. 2:12-MD-02327 MDL No. 2327
THIS DOCUMENT RELATES TO WAVE I	JOSEPH R. GOODWIN U.S. DISTRICT JUDGE

EXPERT REPORT OF MARIA ABADI, M.D.

Prepared by

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Background and Qualifications

After graduating from anatomic pathology residency and serving as chief resident, I completed post-graduate specialty training in Surgical Pathology, Gynecologic Pathology and Cytopathology. It was at this time when I started my employment at Jacobi Medical Center, Department of Pathology, with an academic appointment at the Albert Einstein College of Medicine. I have been at these Institutions during my entire academic career.

I am currently Vice Chair of the Pathology Department, and have been promoted to Professor of Pathology, Clinical, and Associate Professor of Obstetrics and Gynecology and Women's Health (Clinical) of the respective academic Departments at the Albert Einstein College of Medicine. I serve as Director of the Surgical Pathology and Cytopathology laboratories, and oversee an average of 13,000 surgical pathology and 15,000 cytopathology specimens per year; of which 60% are gynecologic cases.

During my academic career, I have acquired extensive experience in Surgical and Gynecologic Pathology. I have been a leading author and collaborator in national and internationally recognized scientific studies with various presentations and publications in peer-reviewed medical journals. Given my day to day practice, I see a significant number of cases displaying pathologic findings which represent most, if not all, variables of normalcy and deviations of expected healing; as well as abnormal tissues and neoplasias. Moreover, during my career I have seen numerous cases of host responses to foreign body materials, including but not limited to different types of surgical sutures, mesh (hernia and urogynecologic repairs), and prostheses.

My opinions that follow are held to a reasonable degree of medical and scientific certainty. This report applies to Ethicon meshes made of Prolene Soft mesh. Attached to this report are my curriculum vitae (Ex. A), which sets out my education and training in detail and lists my publications; a list of the materials I reviewed for this case and materials/exhibits which I will use to support my opinions (Ex. B., which among other things includes photographs, photomicrographs, and pathology slides I have reviewed); my billing rate is $500 per hour; and a list of deposition and trial testimony in the last four years (Ex. C). I expect to review the deposition transcripts of certain of plaintiffs' experts in this case and may further develop my opinions after having done so. Also attached to this

Report is Appendix A (Powerpoint) and Appendix B, which contains my response to the photographs contained in Dr. Iakovlev's General Report.

Overview of Vaginal Histopathology and Physiology

The wall of the vagina is comprised of stratified squamous epithelium, lamina propria, muscularis and adventitia. The squamous epithelium is divided into basal, parabasal, intermediate and superficial cells which, after puberty and before menopause, are several layers thick and contain abundant glycogen. The changes in the thickness and maturation of the vaginal epithelium are cyclic and determined by the predominant effect of either estrogen or progesterone. In contrast to childbearing years, childhood and post-menopause periods are characterized by low levels of estrogen that lead to a significant reduction of the thickness of the epithelium and a loss of superficial and intermediate cells. From more than ten layers thickness, the epithelium is reduced to a maximum of 4-6 layers.

The layer immediately beneath the epithelium is the lamina propria, composed of loose fibro-connective tissue, vessels, nerves and an abundance of elastic fibers. In addition, it contains mostly CD8+ T lymphocytes, and to a lesser extent CD4+ T lymphocytes, mast cells and monocytes. Other inflammatory cells such as neutrophils, macrophages and plasma cells in significant number are less common. Under the lamina propria, there is the muscularis with two ill-defined muscle layers continuous with the myometrium of the uterus. The outermost fibrous layer is the adventitia, where additional blood vessels, lymphatics and nerve fibers are present.

The vagina does not contain glands, therefore, its lubrication derives from other sources: cervical mucus and the breakdown of glycogen by Döderlein bacilli (aka Lactobacillus acidophilus), which are also responsible in maintaining an acidic pH (around 4). This acidic environment protects the tissue from infection. Hormonal imbalances can cause a shift in the pH in the vagina, alteration of local flora and/or fungal infection. Even physiologic changes such as those experienced during menstruation or orgasm can modify the acidity of the vagina. During menopause, the loss of glycogen in intermediate and superficial cells leads to an atrophic vaginitis and increased risk for infection.

Pelvic organ prolapse is the result of a combination of genetic predisposition, age, mechanical stress, hormonal modulation and abnormal extracellular matrix remodeling. The most significant histopathologic changes are evident in the squamous epithelium and fibro-connective tissue: with exposure, friction and irritation, the thickness of the epithelium increases (acanthosis) and the superficial layers of the vagina and cervix undergo keratinization and retention of nuclei (hyperkeratosis and parakeratosis) similar to skin, a process known as epidermalization. Irregular and fragmented elastic fibers are present in the stroma as well as a mild chronic inflammatory response composed of lymphocytes and plasma cells. Studies on collagen and elastin metabolism in women with prolapse and stress incontinence have shown progressive matrix remodeling, degradation of elastic fibers and impaired elastin synthesis.

GENERAL TISSUE RESPONSE TO PROLENE SOFT MESH

1) General Concepts of Wound Healing

Wound healing is a dynamic process that entails complex interactions between different elements including but not limited to cytokines, distinct cell types, and other local and systemic factors. It typically begins with the coagulation stage, which regulates hemostasis and aims to balance signals that trigger the second stage of inflammation. The inflammatory phase starts within minutes to hours of the injury and may last days to weeks. During this stage, there is an upregulation of messengers that protect the wound from infection by attracting and activating predominantly neutrophils / macrophages, which will phagocytize potential pathogens, debride the wound and secrete cytokines and growth factors that control the migration and activation of fibroblasts and endothelial cells. Inflammation is a critical phase in healing as it represents the bridge between the initial tissue injury and the eventual repair. If disrupted, it leads to chronic wounds and ineffective scarring. During the following step of epithelization and angiogenesis, there is production and deposit of the new collagen-containing extracellular matrix and a cellular monolayer that covers the wound surface with compaction of the underlying connective

tissue. Finally, the maturation or remodeling stage will define the patterns in which this new matrix will acquire its ultimate shape and function.

The healing process is affected by age: as we get older, there is decreased collagen density, fewer fibroblasts, increased elastin fragmentation and slower wound contraction. In addition, there are local and systemic factors that will affect the healing process. Included in this category, and especially important, are those conditions that have the final effect of limiting the perfusion and consequently the delivery of oxygen to the healing site. These are predominantly the cases of failing cardiopulmonary health, local edema, ischemia, infection, neuropathy, and vascular insufficiency. Furthermore, malnutrition and catabolic states affect fibroblast proliferation, collagen synthesis, deposit and remodeling. Those individuals who suffer from diabetes have altered immune function predisposing them to infectious complications; also slower collagen synthesis, poorer tensile strengths of wounds, and decreased perfusion because of its associated atherosclerosis and neuropathy. Smokers will bear the direct toxic effects of cigarette ingredients, the vasoconstrictive effects of nicotine, impaired neutrophil function and decreased collagen synthesis. There are additional individual differences in healing response based on idiosyncrasies of the patient. For example, certain patients produce more scar tissue in response to injury than others, while others are predisposed to dense scarring called keloids.

2) <u>Acute Inflammatory Response with Implant</u>

Polypropylene meshes, including Ethicon's meshes made of Prolene Soft mesh, have been used for the treatment of pelvic organ prolapse due to their clinical efficacy and biocompatibility. The latter has been evaluated mainly in animal models and consists of a mild, persistent foreign body giant cell reaction. Like any other inert foreign body material such as carbon or metal, the inflammatory response elicited by polypropylene is non-specific and not T-cell mediated. After implantation, the initial inflammatory response is due to the operative trauma. Platelet aggregation and hemostasis begin immediately after blood vessels are injured to prevent hemorrhage and further tissue damage. Platelets are also responsible for recruiting neutrophils and macrophages through the release of cytokines, platelet-derived and transforming growth factors. Concomitantly, fibrinogen and

other proteins coat the bioengineered material, in this case polypropylene. The fibrin serves as a "model/core" upon which cells migrate and proliferate, and triggers the conversion of monocytes into macrophages. During the acute inflammatory phase, which usually peaks at 24 hours and lasts a few days, neutrophils release oxygen radicals and proteases to clean the wound. The acute inflammatory response is self-contained ending with apoptosis (programmed cell death) and karyorrhexis (nuclear fragmentation) of neutrophils.

3) Chronic Inflammation/Proliferative Phase

The next step in wound healing is the proliferative phase and the formation of granulation tissue. Angiogenesis (new vessel formation) is promoted by vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), platelet derived growth factor, adenosine, tumor necrosis factor-alpha, and the mobilization of endothelial progenitor cells. New vessels are required for blood supply and the delivery of nutrients to the proliferating cells responsible for re-epithelialization. The release of angiogenic factors causes changes in the vessel walls that lead to the release of plasma and the migration and proliferation of endothelial cells to the target area. The proliferating endothelial cells form tube-like structures that will eventually become fully-formed vessels with the restoration of the endothelial cell junctions and basement membrane. The final stage of angiogenesis is modulated by angiostatic factors such as interferon-gamma, nitric oxide, endostatin, angiostatin and angiopoietin-2.

In addition to new vessel formation, the macrophages, bound to the protein (fibrin clot) that coats the mesh, release transforming growth factor β (TGFβ) and other mediators that induce fibroblastic proliferation. Dormant fibroblasts transform into myofibroblasts that synthesize extracellular matrix (ECM), which is initially composed of collagen type III, fibronectin and hyaluronic acid. By the second week, type I collagen will be the one predominantly produced by fibroblasts. Resolution of the inflammatory phase of wound healing is due to the secretion of anti-inflammatory cytokines, transforming growth factors, particularly TGF-A1 as well as prostaglandins.

4) Foreign Body Reaction to Polypropylene Fibers

Since the polypropylene fibers are too large to be phagocytized, the result is the fusion of some macrophages into giant cells that become apposed to the surface of the fibers in an attempt to contain and isolate them from the rest of the tissue. Most cases show only a few or no giant cells around the fibers as well as only a mild to moderate lymphocytic infiltrate. The lymphocytes when present form small aggregates in the vicinity of the fibers, but there is no significant infiltrate between individual fibers or groups of fibers. The lymphocytes and mast cells seen in the submucosa and within the epithelium are ubiquitous to the vagina (surveillance cells) and have no relation to the polypropylene fibers. Evaluation of preoperative and postoperative cell counts show an increase in macrophages and mast cells after mesh implant, but no increase in other inflammatory cells types, particularly those associated with infection. There seems to be no correlation between the levels of inflammation and the presence of pain and/or mesh exposure. (Hill et al. Int Urogynecol J 2015. 26:591-5)

5) Remodeling of Matrix and Fibrosis

The extracellular matrix synthesized by fibroblasts matures and undergoes remodeling. Type III Collagen is substituted by Type I and remodeling is achieved through enzymes such as metalloproteinases and transforming growth factor β (TGFβ). Incorporation of the host's cross-linked collagen into the mesh provides tensile strength and support. After 6-7 weeks, the activated fibroblasts/myofibroblasts undergo apoptosis. Net collagen deposition seems to peak 6 weeks after surgery and by this time the wound acquires approximately 50% of its tensile strength. The balance between collagen synthesis and remodeling may continue even a year after injury. It is important to emphasize that despite effective healing, the tensile strength of the tissues achieved after wound repair is not the same as before the injury.

6) Impaired Healing

Chronic inflammation is part of normal healing; however, imbalances in the process can lead to pathologic non-healing chronic wounds. Conditions such as Diabetes Mellitus, infections, smoking, as well as the patient's genetic makeup and idiosyncratic response, can lead to wound healing failure. These conditions are characterized by excessive inflammation (much more prominent than the degree typical seen in response to Prolene Soft mesh), impaired angiogenesis leading to poor perfusion and nutrition, and increased release of collagenases that affect matrix synthesis and remodeling.

PROLENE SOFT PROPERTIES

Porous (> 75 microns) lightweight materials have been shown to facilitate cell proliferation and tissue ingrowth. The Prolene Soft mesh with its large pore size (> 1,000 microns) facilitates the passage of fibroblasts and the deposition and integration of the patients' collagen into the framework. Masson trichrome-stained sections reveal that the deposition of mature collagen is evident around the fibers and blends seamlessly with the surrounding stroma. There is no evidence of encapsulation or hypertrophic, nodular scar formation such as the one seen in porcine collagen coated meshes, porcine dermis or cadaveric grafts. Furthermore, the macroporous knitted design facilitates cellular adherence and vessel ingrowth into the mesh. Vessel ingrowth is an important factor in the maintenance of nutrient delivery to the tissues. Monofilament mesh typically elicits a milder inflammatory response and foreign body giant cell reaction than multifilament mesh.

Prolene Soft is a Type 1 macroporous mesh. The large pore size of the Prolene Soft used in Ethicon's Prolift has been found to reduce the risk for bacterial colonization and the potential for infection. The infection rates associated with the Prolift procedure are low. (Diwadkar GB, Barber MD, Feiner B, Maher C, Jelovsek JE. Complication and Reoperation Rates After Apical Vaginal Prolapse Surgical Repair. Obstet Gynecol 2009; 113: 367-373)

The polypropylene mesh serves as a framework for collagen deposition in order to provide support to a weakened pelvic floor. The expected histologic findings, once the healing process is completed, are total integration of the mesh to the tissues of the host, mild chronic inflammatory response, without active inflammation, and focal foreign body giant cell reaction. Histologic evaluation of excised meshes provides information regarding the type of inflammatory response (chronic, acute, foreign body reaction, etc), the status of the mucosa (intact or ulcerated, atrophic or mature), the quality of the tissues (healthy or necrotic) and whether there is superimposed infection. Microscopic evaluation without correlation with specific biomarkers and tests does not assess cytotoxicity, activation of pro-inflammatory mediators, response of nerve receptors to stimuli or perception of pain by the central nervous system.

HISTOLOGIC PROCESSING OF EXCISED MESH

Currently, there is no uniformity in the pathologic evaluation of explanted mesh material. While some laboratories perform only a gross evaluation of the specimens, others submit the tissues entirely for histologic evaluation. Not all surgically removed meshes are adequately fixed in 10% buffered formalin and therefore, can show evidence of autolysis and desiccation.

The polypropylene fibers are subjected to significant manipulation during surgical excision, gross evaluation and dissection as well a tissue processing. The effects of cutting and pulling with scalpel, forceps and other surgical instruments and the dehydration caused by hours in xylene and different concentrations of alcohol can lead to artefactual retraction, folding and damage to the fibers. After 12 cycles of at least 5-6 hours in the tissue processor, the specimen is embedded in paraffin and then cut with a microtome to generate 5 micron sections that will again be placed in degrading alcohols and xylene solutions during the standard hematoxylin and eosin (H&E) staining. The fact that some intact fibers can still be seen demonstrates the effective integration of the host's tissue into the material.

RESPONSE TO PLAINTIFFS' PATHOLOGY EXPERT

I have reviewed the expert report of Dr. Vladimir Iakovlev and my opinions are as follows:

1) Pain and nerve damage:

Chronic pain is defined as pain that lasts beyond the expected time for healing. Pain has been classified in two main different types: Nociceptive and neuropathic. Nociceptive pain occurs when a nerve fiber is particularly sensitive to tissue damage, such as that caused by trauma, inflammation or surgical intervention. This type can be somatic (sharp and localized), or visceral (dull, vague and deep). Neuropathic pain is due to abnormalities in the nervous system, central or peripheral, and one of the classic examples is the neuropathic pain of the patient with Diabetes Mellitus. Pain is a complex process with a major subjective component that cannot be diagnosed by review of histology. Furthermore, it is affected by the patient's previous experience with pain (sensitization), and by concomitant conditions such as diabetes, other types of neuropathy, psychiatric conditions and psychosocial issues.

According to Dr. Iakovlev, the pain experienced by the plaintiffs is the result of direct irritation of nerve branches by the inflammation caused by the mesh, or entrapment of nerves by the scar tissue present within or around the mesh. However, the mere presence of inflammatory cells or scar tissue does not directly correlate with the quality, type and intensity of pain. Activation of nociceptors requires the presence of pro-inflammatory mediators such as: cytokines, chemokines, bradykinin, prostaglandins, histamine, and cellular ions and growth factors. Histological examination of explanted mesh material does not provide this information nor does it reveal cytotoxic effects on nerve receptors or mechanical irritation of fibers. Although nerves can be identified among mesh fibers, their specific type and function cannot be established in regular hematoxylin and eosin-stained sections. Immunohistochemical stain for S-100 protein is of limited value since it is not specific for nerve tissue, but can also stain other cells such as dendritic cells, adipocytes and myoepithelial cells. Since many of the explanted meshes consist of dry

tissue, there is propensity for high background immunostaining (too strong and uneven) that can cause false positive and unreliable results.

In his report, Dr. Iakovlev purports to illustrate the presence of distorted nerve fibers within the mesh. Unless characteristic features of traumatic neuroma are present (non-neoplastic mass of disorganized nerve fibers surrounded by perineurium within myxoid or fibrous stroma, with signs of axonal regeneration), the distortion of nerve fibers in tissue could be due to manipulation and unrelated to the mesh. In any event, traumatic neuromas are often the result of injury during any surgery. Dr. Iakovlev has provided no reliable evidence that the distorted appearance of these nerves leads to pain.

2) Mesh stiffening, contraction and shrinkage:

The development of scar tissue, contraction and shrinkage reported with mesh implant is not due to the fibers, but rather to the normal healing process of collagen deposition and remodeling. The mesh acts as a framework so once the collagen has been laid and matured, it serves as a support system to correct the pelvic organ prolapse. Fibrosis is the result of wound healing, and occurs post-surgically, with or without mesh. Abnormal healing processes resulting in hypertrophic scar tissue are secondary to underlying conditions such as diabetes, aging, smoking, vascular disease among others, and not to the quality of the material. Elasticity and tensile strength are lost after tissue injury, regardless of the type of injury (infection, vascular, trauma), and do not revert to pre-injury levels even in the context of normal wound repair.

3) Deformation and Mesh Migration:

From a pathology point of view, it is speculative for Dr. Iakovlev to opine that any given mesh has migrated. Purported deformation and migration of fibers is the result of external forces applied to the material such as pulling and cutting by the surgeon explanting the mesh, by the manipulation of the histology staff or by the numerous reagents and chemicals used in laboratory processing (not limited to formalin). Moreover, some of the explanted meshes and surrounding tissues were never fixed in formalin resulting in a dry and brittle specimen. On microscopic evaluation, most sections show avulsed, displaced and folded fibers, or only spaces where the fibers used to be. All of these

findings are artefactual in nature and do not provide any real information as to the migration or deformation of the mesh in vivo.

In contrast to Dr. Iakovlev's claims, the gross examination of explanted mesh does not represent at all how the mesh was positioned in vivo. The macroscopic pathological examination of an explanted mesh reveals deformation caused by the surgeon at the time of excision.

4) Polypropylene Degradation:

In some of the histologic sections, an outer surface layer appears on the Prolene fibers with features distinct from the core. Dr. Iakovlev has claimed this is degraded "bark" from the mesh. Dr. Iakovlev's methods do not reliably rule out that changes in the outer surface layer represent protein coating. Although the layer sometimes (but not all the time) shows birefringence, it also stains with Periodic Acid Schiff (PAS) stain, indicating it may be protein based. Dr. Iakovlev's observations and testing also do not rule out that this "bark" is an artifact of processing and/or microtomy. Importantly, tissue processing uses harsh chemicals, such as xylene.

In my review of slides from explanted mesh and Dr. Iakovlev's photographs, I have seen nothing that indicates this outer surface layer has any clinical significance. The tissue response to this outer layer is normal and, as I have described throughout this report, the inflammatory and foreign body reactions range from none to mild, which is the expected response to the mesh implant. Evaluation of polypropylene sutures reveals the same findings (including superficial fragmentation) and those are used regularly in diverse and complex surgical procedures, such as cardiac bypass with no adverse effects. Even if Dr. Iakovlev were correct, the core of the fiber is preserved. This is important because, despite surgical manipulation during removal, the fiber core retains its integrity.

Dr. Iakovlev also claims that the superficial "degraded" layer of the fiber (so called "bark") increases in thickness with time and that this change plateaus "in vivo" after 5-6 years. This observation is based only on explanted meshes from patients with symptomatology without comparison with controls (patients with successful mesh implantation and no symptomatology). Without a proper randomized study, this is only

hypothetical, descriptive and speculative. He does not provide a scientific explanation as to why the process is self-limiting and how that would affect the integration of the mesh into the tissues or its ultimate function, since he admits that the main component of the fibers remains intact.

5) Degenerative calcifications:

Dystrophic calcifications are defined as the deposition of insoluble calcium salts in sites of tissue damage (such as the one caused by surgical procedures or trauma). They often occur in areas of fat necrosis and are not triggered by the mesh. Some systemic disease predispose to the development of dystrophic calcifications such as autoimmune disorders.

6) Mucosal erosion and tissue edema:

Due to low estrogen levels, the vaginal epithelium of postmenopausal women becomes thinner and dry; it is therefore more susceptible to mechanical trauma, erosion, inflammation and infection (atrophic vaginitis). Women with vaginal atrophy, with or without mesh, experience vaginal dryness, burning, pruritus, dyspareunia and vaginal discharge. Superimposed bacterial infections are common due to changes in the vaginal pH (> 5). Other conditions such as desquamative inflammatory vaginitis, which often occurs in postmenopausal women can cause the same symptoms and are associated with, acute and chronic inflammation as well as erythema (red patches) and erosion of the squamous epithelium.

Dr. Iakovlev describes vascular obliteration in the “mesh-scar plate”. The obliteration is due to fibrointimal muscular hyperplasia, a common change seen in vessels of postmenopausal women. “Mesh scar plate” is terminology used by Dr. Iakovlev to presumably imply there is encapsulation of the mesh fibers but what is seen is collagen around fibers, which is the expected outcome. The degree of fibrosis depends on the patient’s inflammatory response, which is affected by the patient’s comorbidities (Diabetes mellitus, hypothyroidism, smoking history among others).

Summary:

Dr. Iavkovlev's conclusions that all of the pathological changes seen in these patients are triggered by the polypropylene mesh are speculative and not supported by scientific evidence. The histological findings in these cases are multifactorial: the result of a combination of aging, predisposing conditions, surgical interventions and wound healing. In most cases, microscopic evaluation reveals the expected changes of a focal and stable foreign body reaction and mild chronic inflammation associated with monofilament mesh implant. The collagen present around fibers does not show encapsulation and the surrounding tissues appear well vascularized with no evidence of necrosis, acute inflammation or infection. Dr. Iakovlev's allegation that a few microns of the outer surface layer on the mesh degrade is not supported by reliable scientific evidence. Even if his theory were true, the outer surface layer has no clinical significance.

Regarding symptomatology, there is no direct correlation between histologic findings and clinical presentation due to the fact that pain is a complex process influenced by anatomical, chemical and psychosocial factors.

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Appendix A

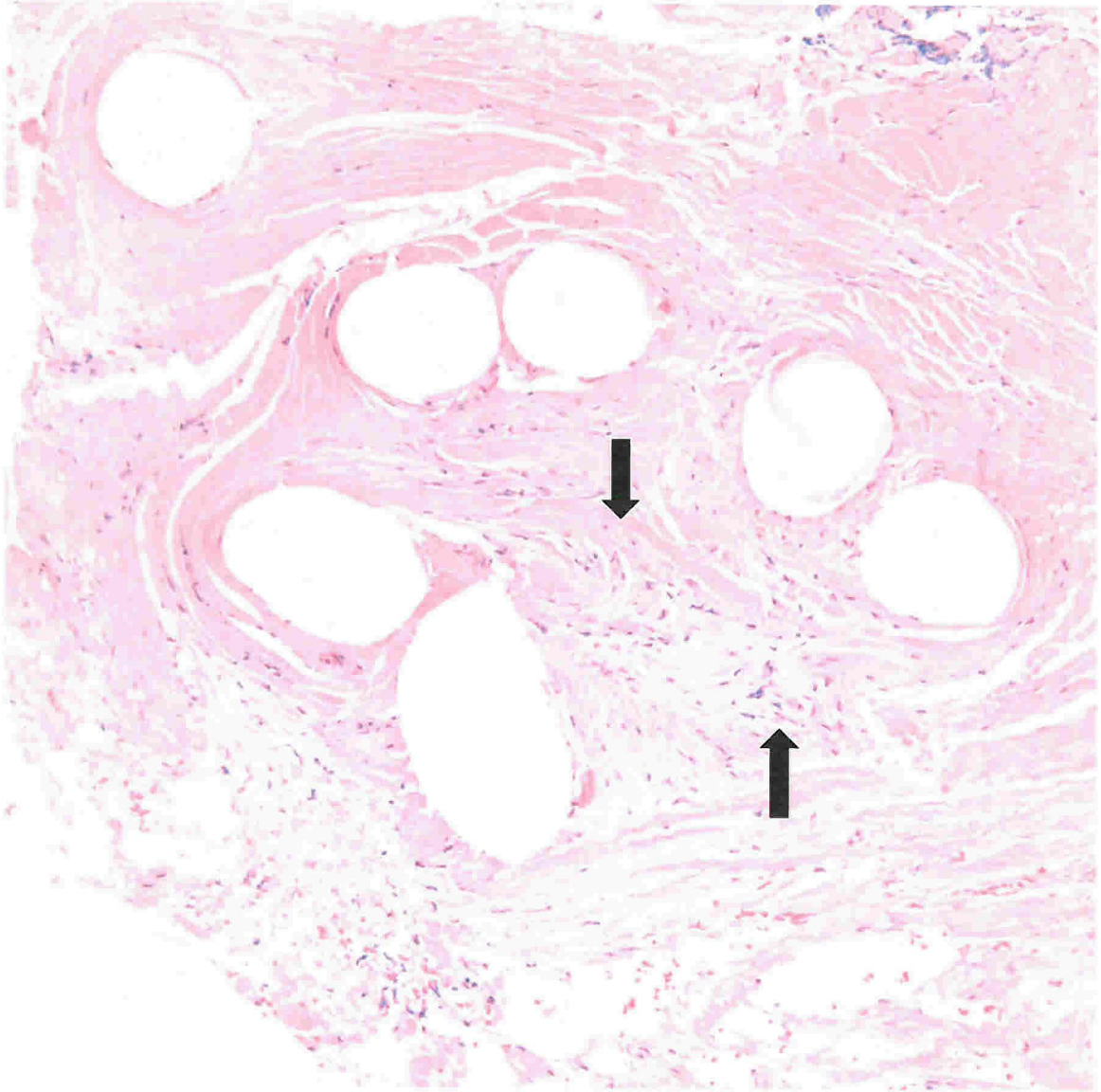

Figure 1.
The mesh fibers are surrounded by fibrous tissue and there is minimal chronic inflammation (arrows). H&E stain, 20X

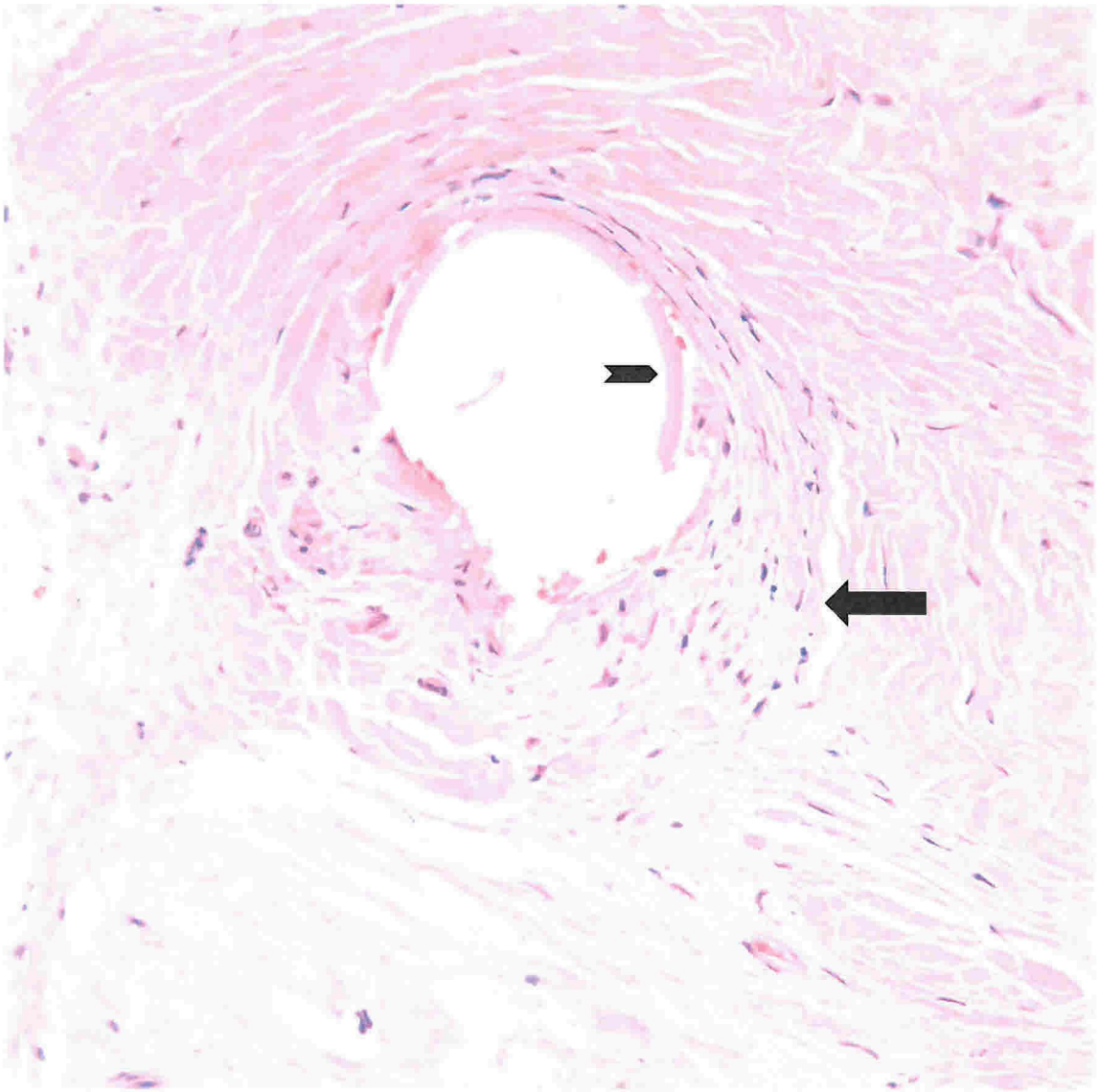

Figure 2.
Individual mesh fiber with mild chronic inflammation (arrow). Dr. Iakovlev's alleged "bark" is marked by the chevron. Note there is no associated foreign body giant cell reaction.
H&E stain, 40X

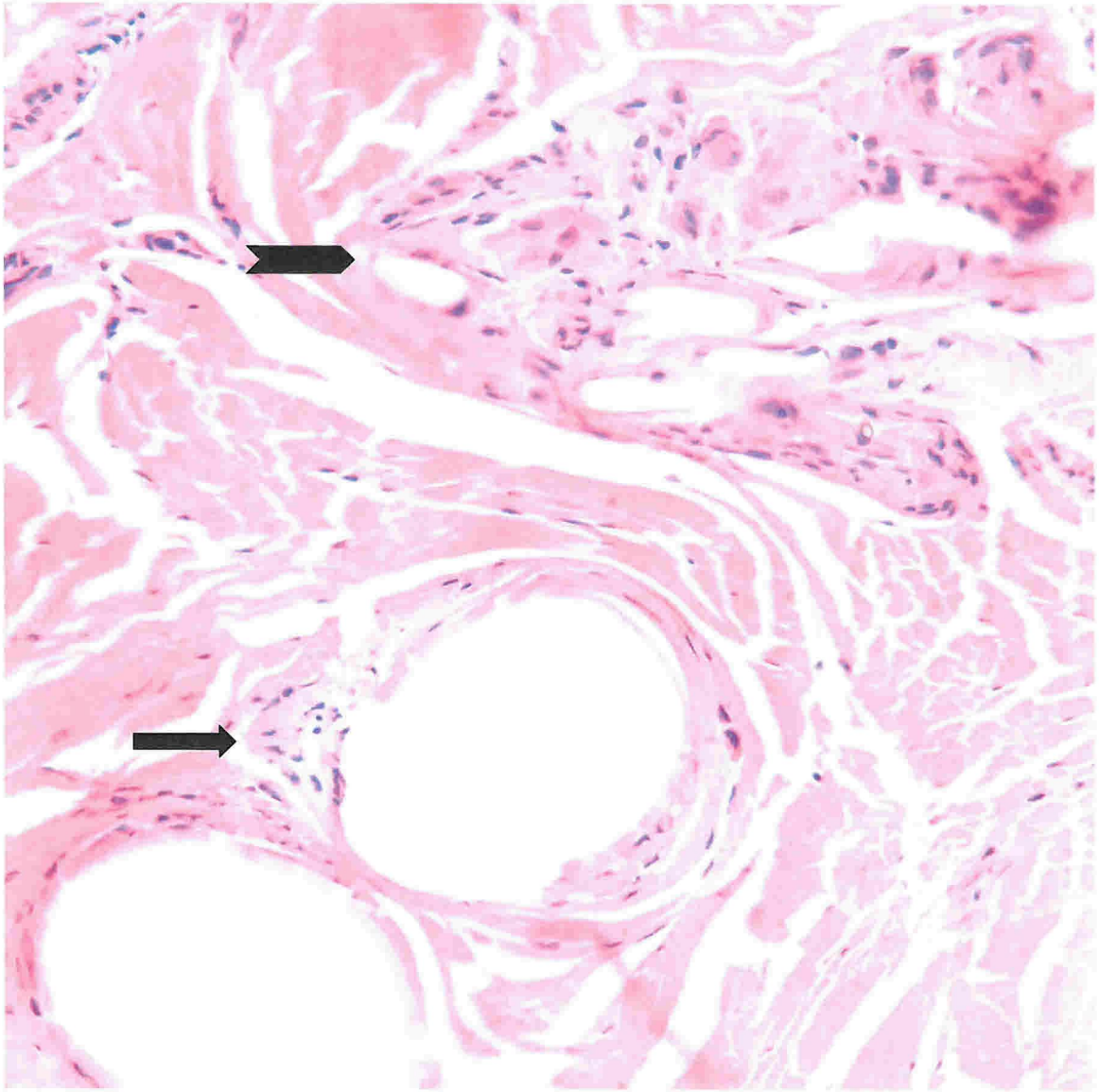

Figure 3.
Mild chronic inflammation around mesh fibers (arrow) in contrast to florid foreign body reaction against suture material (chevron)
H&E stain, 40X

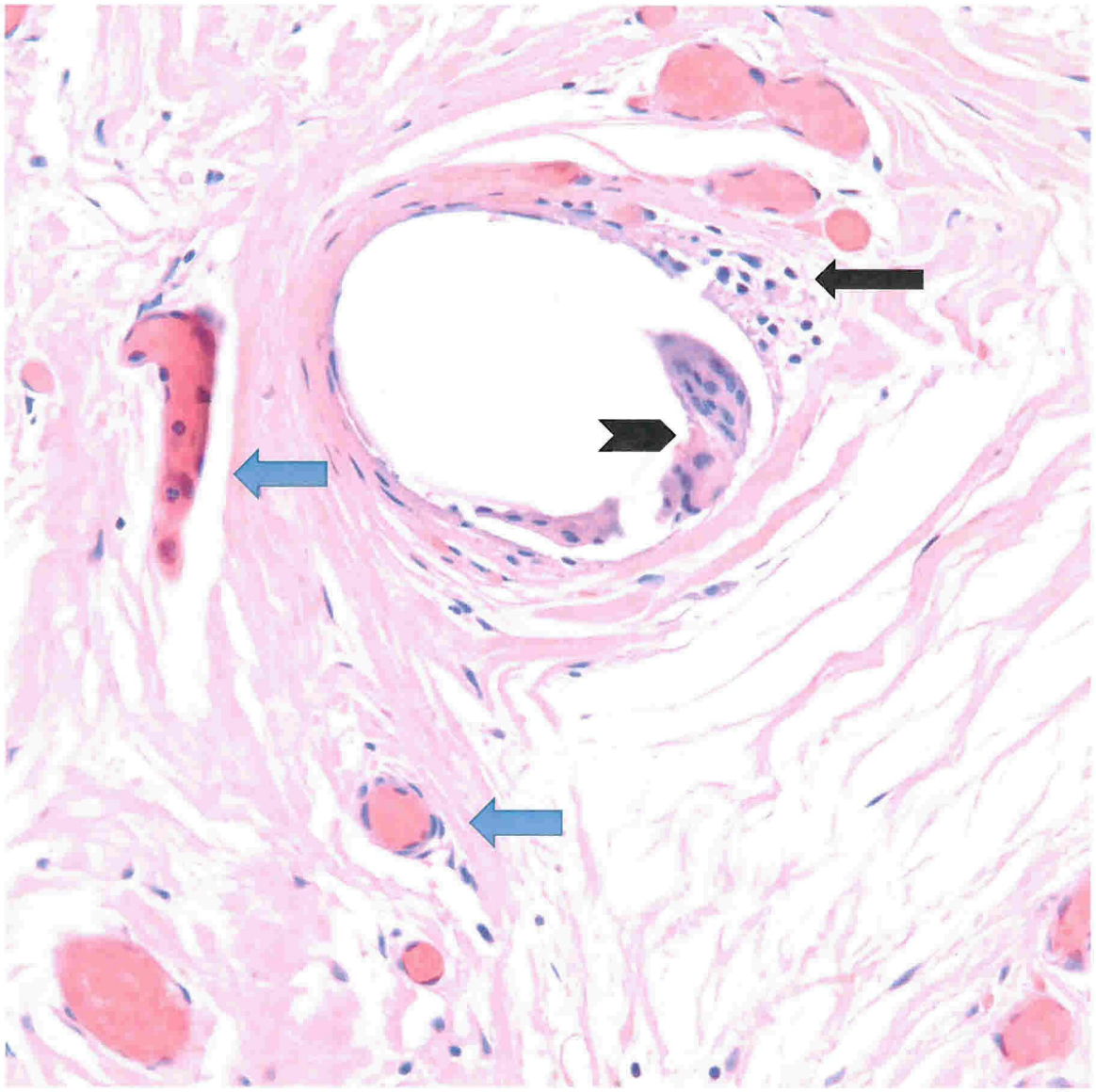

Figure 4.
Mild lymphocytic chronic inflammation (black arrow) and focal foreign body giant cell reaction (chevron) around mesh fiber. There are healthy vessels present adjacent to the fiber (blue arrows)
H&E stain, 40X

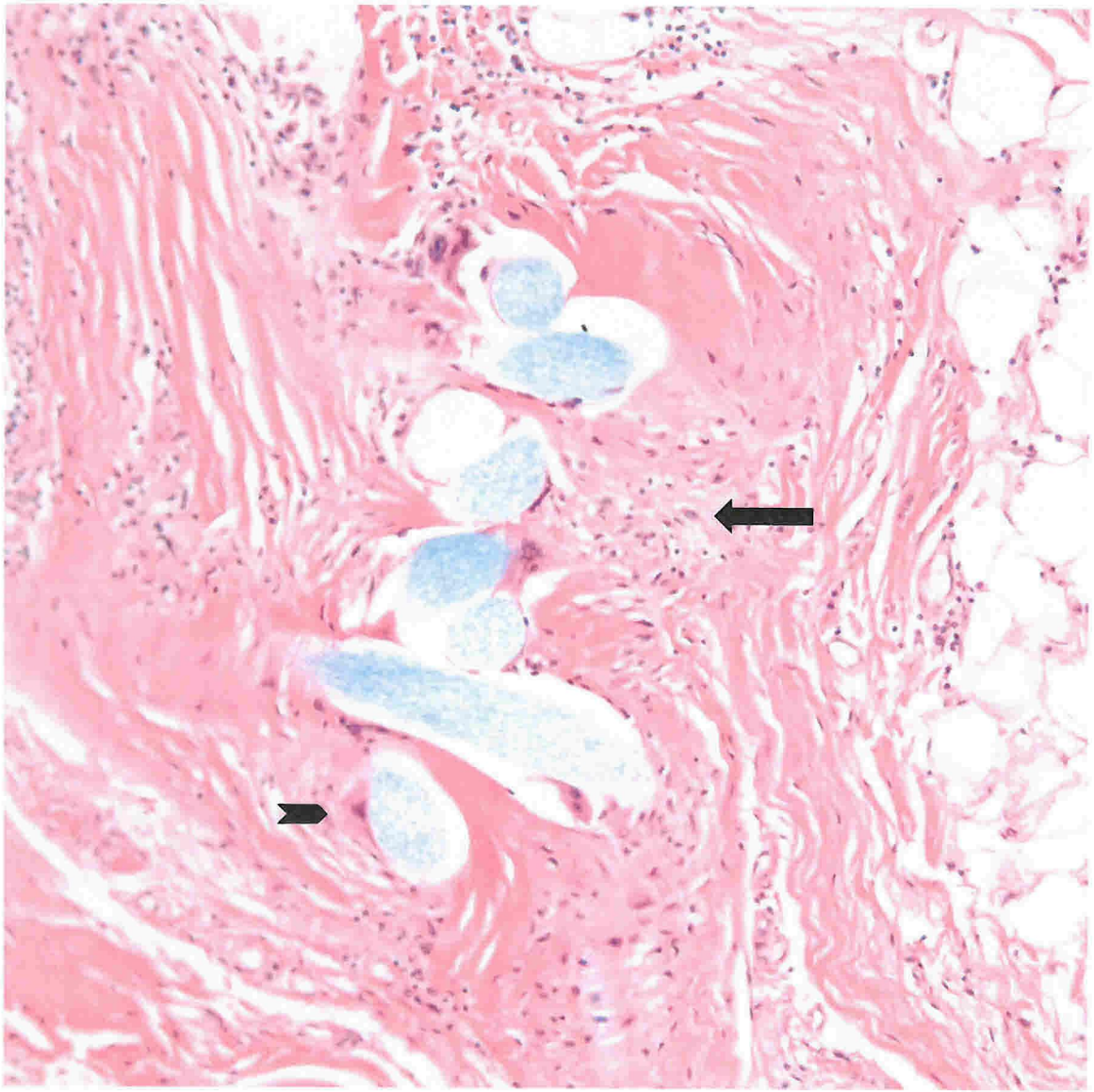

Figure 5.
Polypropylene suture in a cardiac bypass specimen. The inflammatory response with the polypropylene suture is the same as with the mesh: mild chronic inflammation (black arrow) with occasional foreign body giant cells (chevron).
H&E stain, 10X

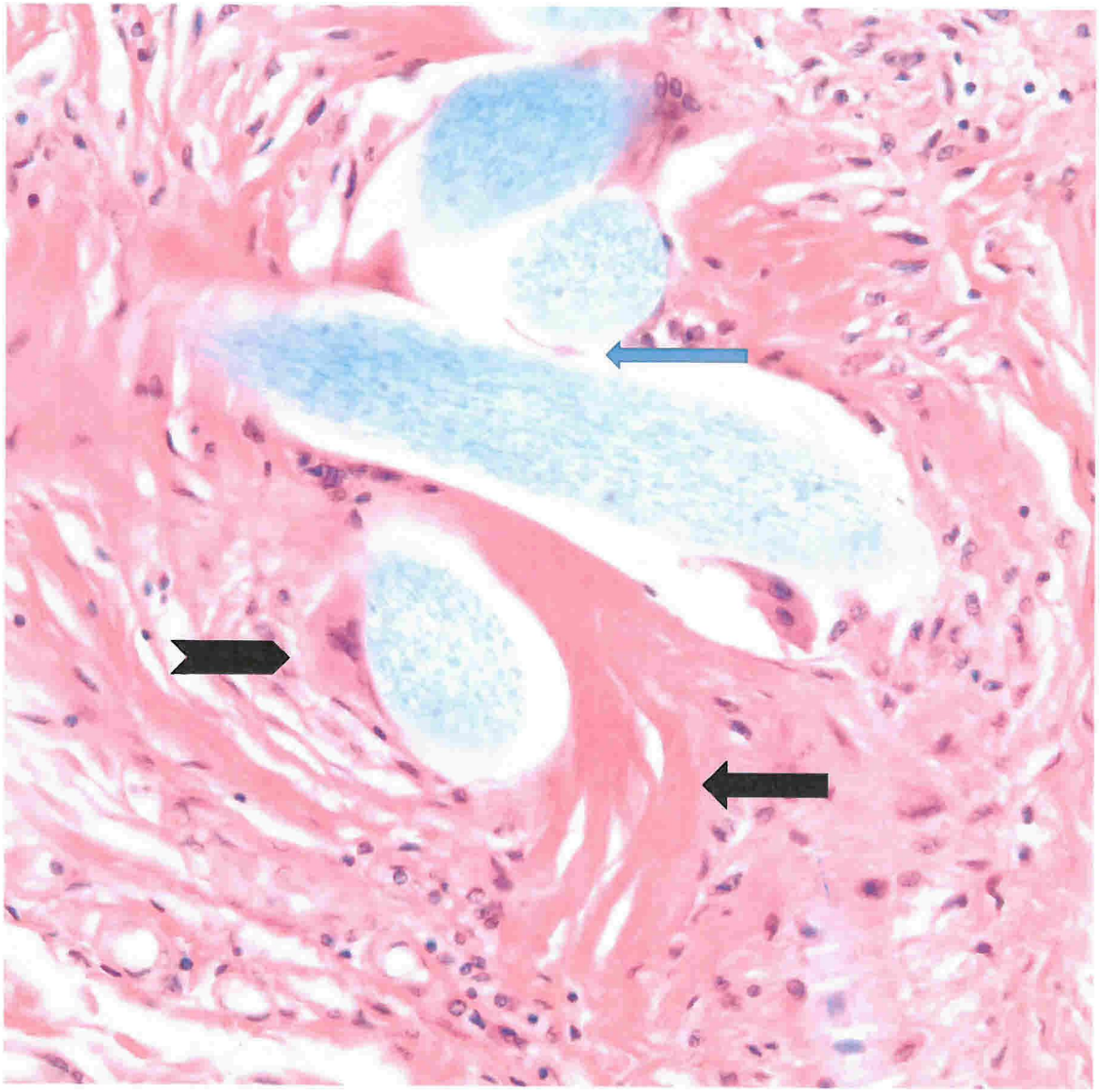

Figure 6.
Foreign body giant cell reaction associated to polypropylene suture in a patient with coronary bypass (CABG) (chevron). The polypropylene suture is also surrounded by fibrous tissue (arrow) in the same manner as in the pelvic mesh cases. Changes in the surface layer are also seen (blue arrow)
H&E stain, 40X

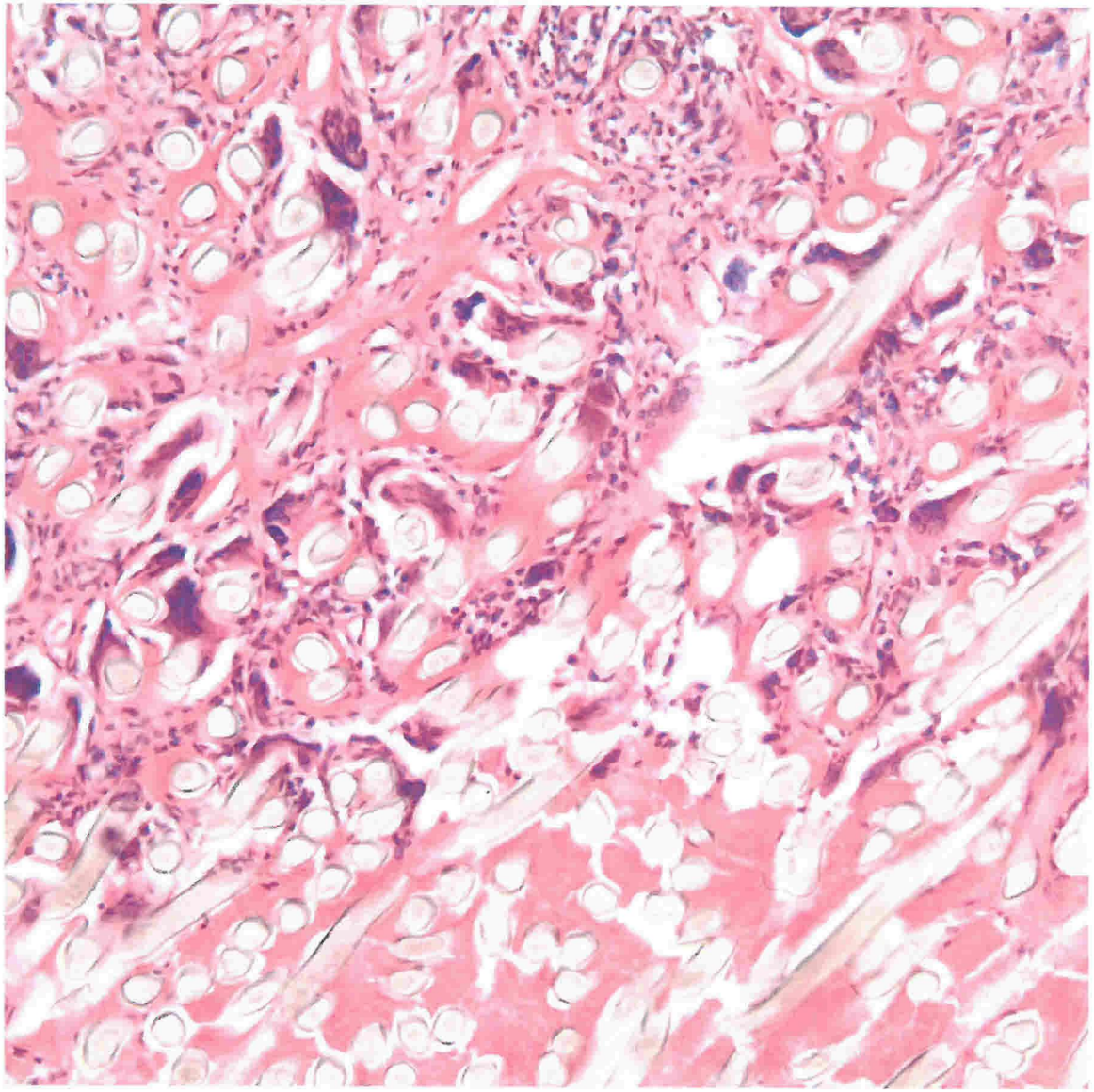

Figure 7.
Florid foreign body giant cell reaction against Dacron fibers used as a pledget in a cardiac coronary bypass (CABG). The florid foreign body reaction is expected and causes no harm to the patient.
H&E stain, 10X

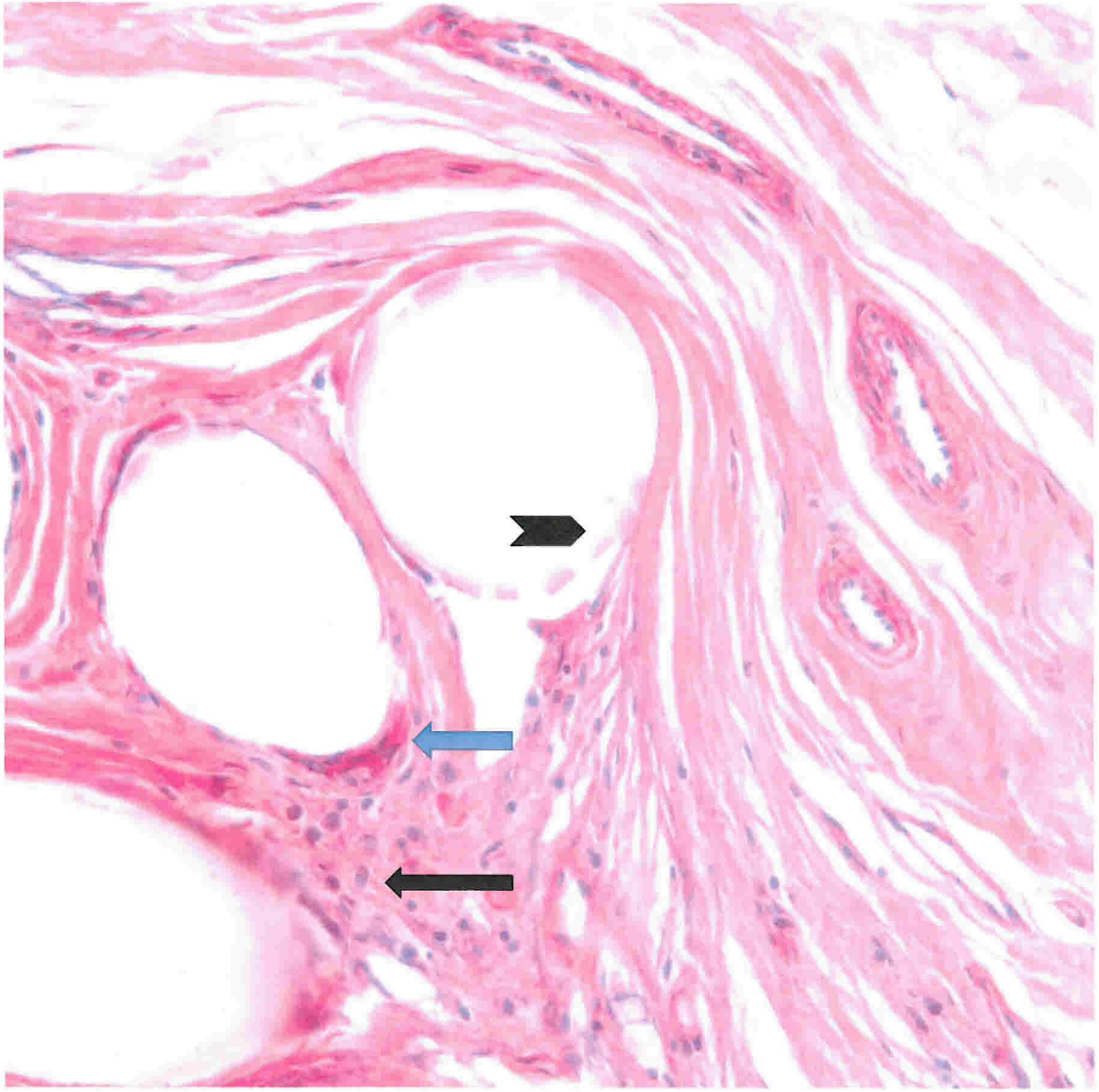

Figure 8.
Photograph showing Dr. Iakovlev's alleged "bark" (chevron). The staining with Periodic Acid Schiff (PAS) is positive, likely due to the presence of glycoprotein, but uneven. Just a few lymphocytes (black arrow) and rare foreign body giant cells (blue arrow) are present.
PAS stain, 40X

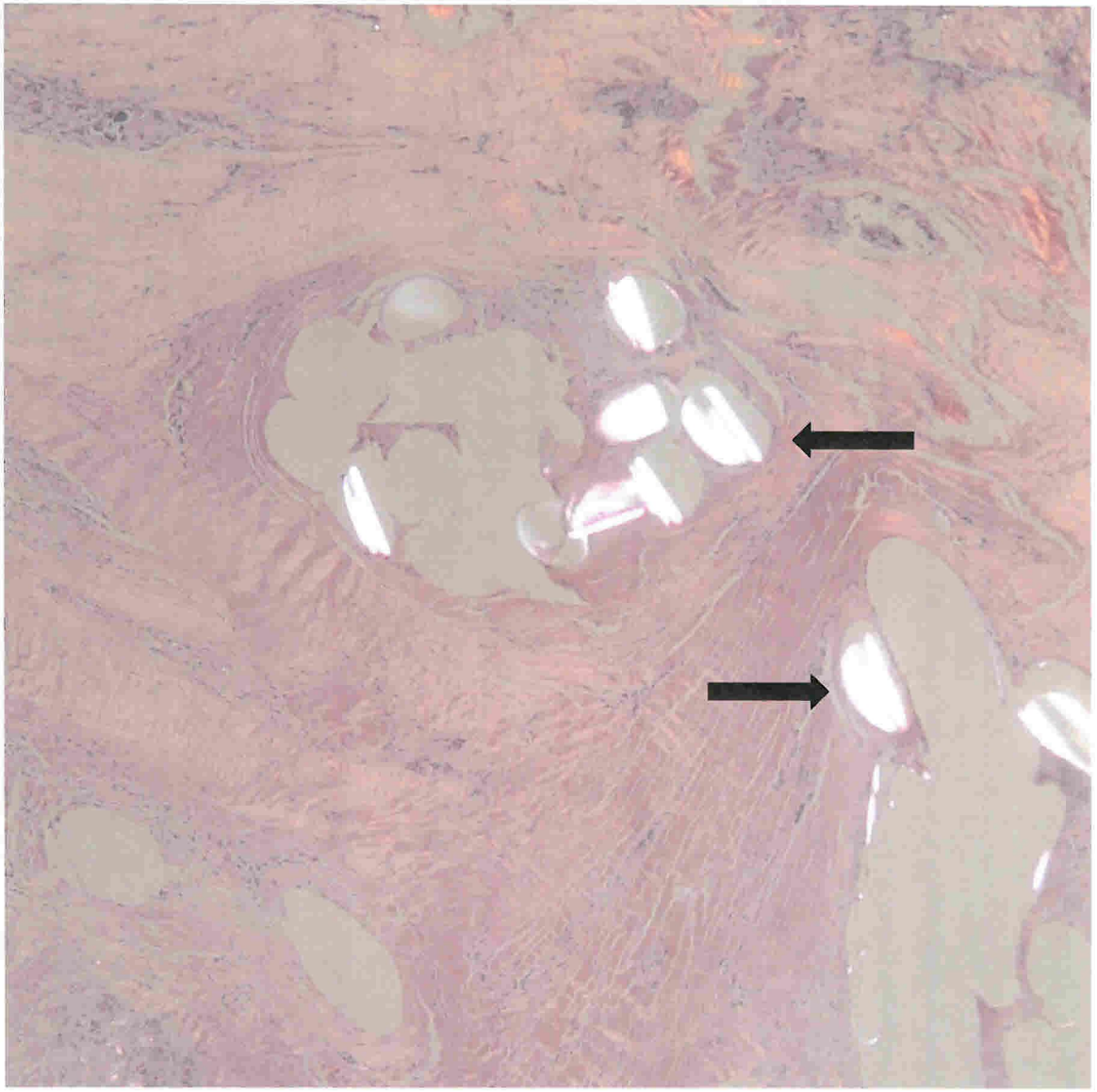

Figure 9a.
Folded and deformed mesh fibers under polarized light (arrows). The deformation occurs during surgical excision as well as during laboratory processing
H&E stain under polarization, 10X

Figure 9b.
Deformation of fibers in a histologic section under polarized light. The polypropylene fibers are birefringent. Some of the fibers are displaced. These changes are the result of manipulation and do not reflect the status of the mesh in vivo.
H&E stain under polarized light, 40X

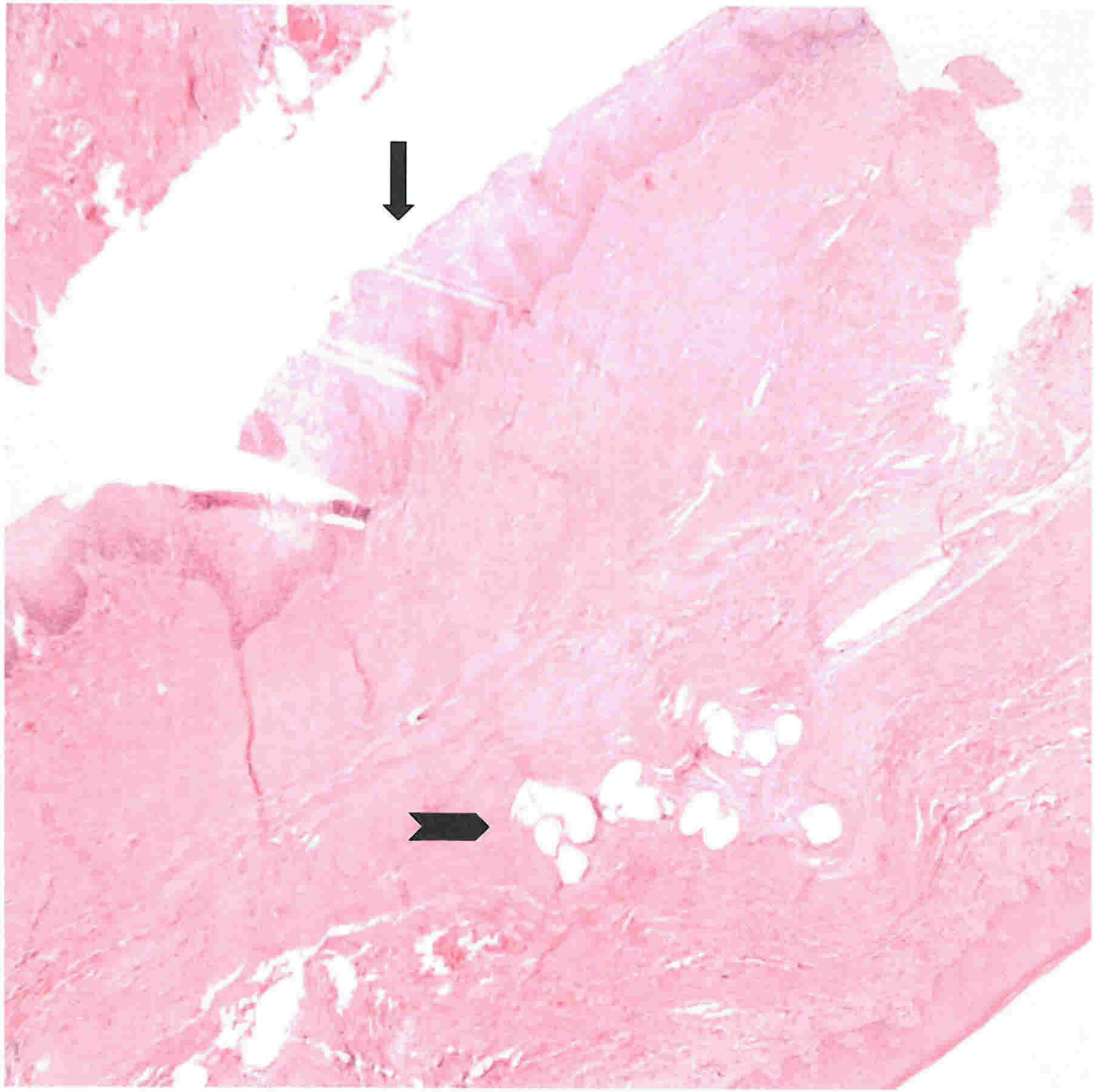

Figure 10a.
Vaginal squamous mucosa with epithelium of normal thickness (arrow). The mesh fibers are present in the submucosa (chevron) with no evidence of inflammation. Notice the evenness of the fibroconnective tissue with no evidence of encapsulation.
H&E stain, 4X

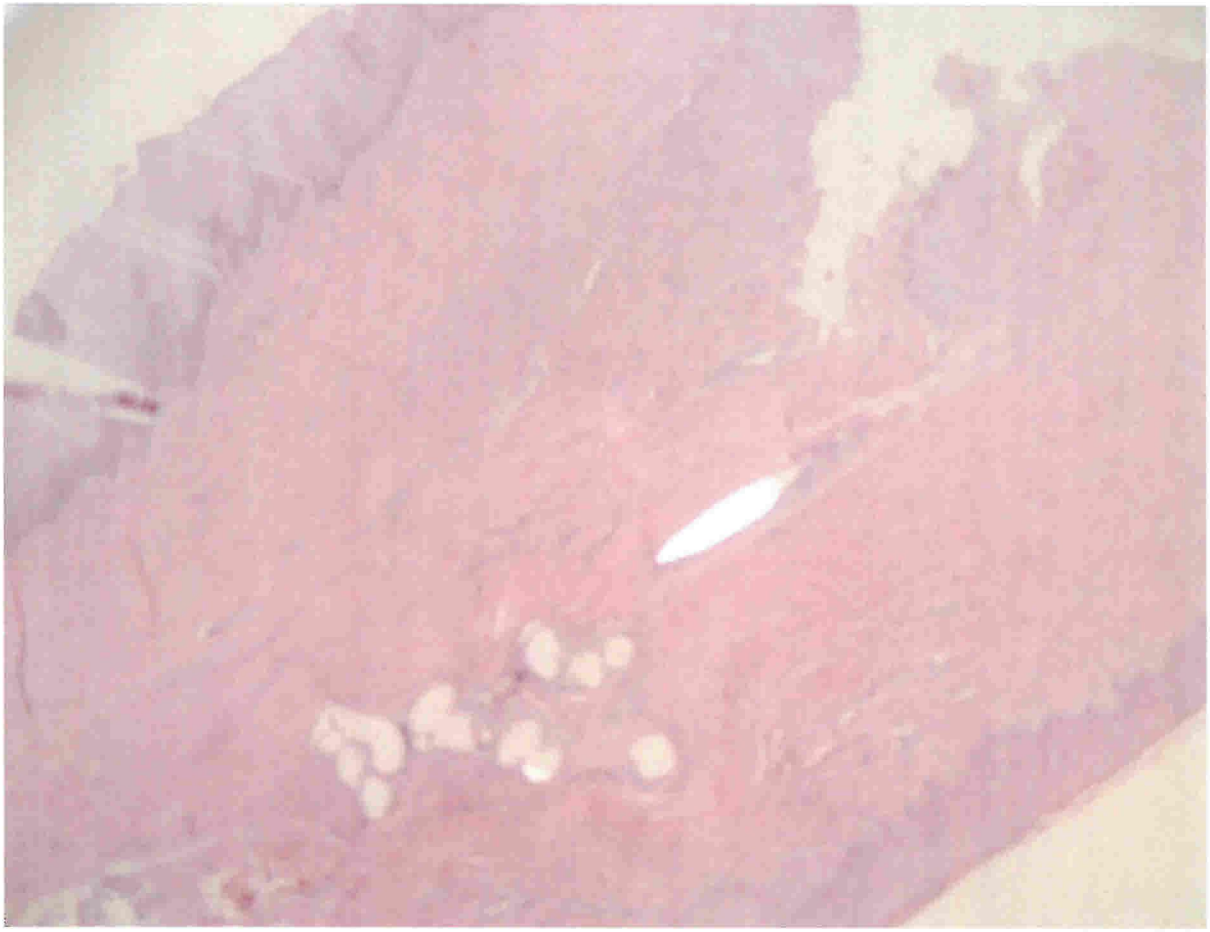

Figure 10b.
Same section as in figure 10a, under polarized light demonstrating the presence of the mesh polypropylene fibers in the submucosa away from the surface squamous epithelium.
H&E stain under polarized light, 4X

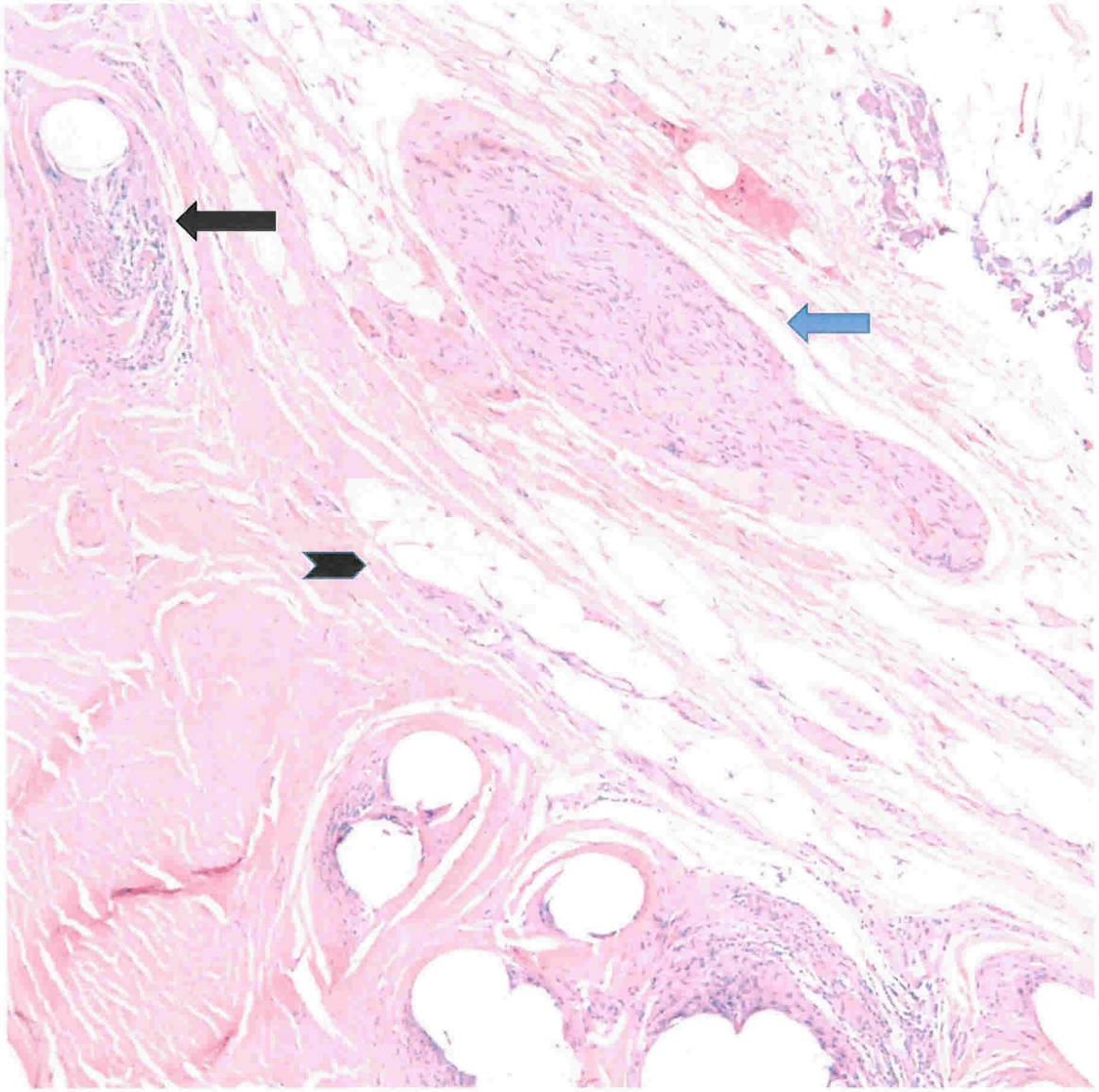

Figure 11.
Mesh fibers surrounded by a chronic inflammatory infiltrate limited to the vicinity of the fibers (black arrow). There is a smooth transition from the fibrous tissue around the fibers and the adipose tissue (chevron). The nerve (blue arrow) is unremarkable and uninvolved by the fibers.
H&E stain, 4X

Appendix B

Response to Plaintiff's Expert Photographs

General Comments:

Evaluation of Dr. Iakovlev's photographs is limited by the following factors:

1) Alteration of the pictures by arbitrary addition of computer generated colors not present in the original histologic sections or stains;
2) Incorrect magnifications in many of the photographs;
3) Use of measurement indicators without explanation;
4) The majority of the pictures of various immunohistochemical stains do not have the H&E stained counterparts for comparison or assessment of morphology; and
5) There is no mention of the quality of the controls for the immunohistochemical stains.

Figure set 1a-1c:

The photographs illustrate the presence of chronic inflammation and foreign body giant cell reaction around mesh spaces and fibers. Although the quality of the pictures does not allow identification of specific inflammatory cells, other than the occasional giant cell, the infiltrate is mild and limited to the immediate vicinity of the fibers.

Figures set 2a-2g:

These photographs are labeled "Fibrous bridging and scar encapsulation". There is no encapsulation. There is fibrous tissue around the mesh fibers as is expected with this material. The mesh creates a framework for the deposition of collagen to provide strength to the pelvic floor. In figure set 2g, a smooth muscle actin stain has been performed to show the presence of smooth muscle. The picture of the immunohistochemical stain (below the photograph of the H&E-stained section) has been modified by adding colors selectively. The background of the immunohistochemical stain is high, but despite these artefacts, it is evident that the walls of vessels between the fibers are staining, which indicates that the areas between the fibers are vascularized. In addition, the fibrosis is limited only to the periphery of the fibers. Smooth muscle is immediately adjacent.

Figures set 3 and 4 (3a-3h and 4a-4e):

These two set of photographs are meant to show damage to the nerves and ganglia by the mesh. Even though the pictures show distorted nerve fibers and ganglia, the distortion could be post-surgical or the result of manipulation during excision of the mesh, or histologic processing. Without special stains to evaluate axonal damage, it is not possible to conclude real damage to the nerve. From figure 3d – 3h, there are no H&E sections included

to evaluate morphology. S100 immunostaining is non-specific and insufficient as the sole immunohistochemical stain or method used to evaluate neural injury.

Figure set 5.

This figure represents normal appearing mucosa. The fibers are located away from the epithelium.

Figure set 6 (6a-6d)

The vessels in this set of photographs are totally unremarkable. They do not show any evidence of congestion or dilatation. All the vessels shown are of similar caliber. Of note, edema, congestion and mild dilatation are seen in the context of surgery due to hemostasis and manipulation. Several areas marked "edema" are actually loose connective tissue, not edema

Figure set 7 (7a-7c)

These figures are labeled "Involvement of striated muscle by the mesh" (7a and 7b) and "Scarring of striated muscle at the mesh" (7c). This set of pictures has a very low quality. In addition of having been modified by computer, the magnification is too low to evaluate the status of the muscle fibers. There is no trichrome stain to support the claim of "scarred muscle".

Figure set 7d-7g

The S-100 stain only highlights the presence of nerve fibers. These photographs do not show any evidence of muscle damage There is no H&E stain to evaluate degeneration/regeneration of muscle fibers or inflammation around fibers. The desmin stain in figure set 7g. is of no additional value.

Figure set 8 (8a-8f)

These photographs of smooth muscle actin attempting to show involvement of smooth muscle by the mesh show marked background staining, likely due to dryness of the tissue or thermal effect. Morphology cannot be evaluated in these pictures due to marked artefactual distortion and staining.

Figure set 9 (9a-9b)

Arterial obliteration in post-menopausal women is a common finding and of no clinical significance. Damage of the arterial wall is better evidenced with the use of elastic stain, which has not been provided. The capillary thrombosis photographed in figure set 9b, page 64 is acute and occurred during the surgical excision of the mesh.

Figure sets 10 and 11

These sets attempt to illustrate curling and folding of the mesh. The folding and curling of the mesh seen after the specimen has been excised (grossly or microscopically) does not provide information regarding the status of the mesh in vivo, especially because the mesh has sustained significant manipulation during surgical removal and laboratory processing.

Figure set 12 (12a-12h)

Erosion of the squamous mucosa in postmenopausal women is common, with or without mesh, as is the presence of bacteria in the vagina. Hormonal changes leading to thinning of the epithelium, pH and bacterial flora increase the risk of ulcerations and infection.

Figure set 13-19

Using these sets of photographs, Dr. Iakovlev claims that polypropylene degradation occurs in vivo and that in fact it plateaus after 5-6 years. In histologic sections, the outer surface on the polypropylene fiber shows fragmentation and its thickness is only a few microns. What he labels "non-degraded core", the main portion of the fiber is intact and smooth. Dr. Iakovlev's theory and photographs do not reliably show what the actual composition of this outer surface layer is. Although the layer is partially birefringent, it also stains with Periodic Acid Schiff (PAS) stain suggesting that it contains glycoprotein. In any event, the cracking and fragmentation of this layer has no clinical significance. It occurs in polypropylene sutures as well with no adverse effects. They are commonly used in cardiac bypass surgeries for their durability and strength. The inflammatory response that they elicit in the cardiac tissues is identical to that seen with the polypropylene mesh in vaginal tissues, persistent but mild chronic inflammation and foreign body giant cell reaction. Dr. Iakovlev uses very high magnification to show the relationship of the giant cell to the mesh fiber (see for example figure 13c, 100x). It is evident that the giant cell is only apposed to the fiber, as it occurs with foreign material. The giant cell reaction is localized, it does not surround the entire periphery of the fiber and there is no evidence that giant cells are present along the entire length of the fiber.

Dr. Iakovlev also claims that this outer surface layer has nanopores that harbor bacteria, but none of the photographs show evidence of bacteria within the cracks or an acute inflammatory response. In figure 18e, he shows a multifilament suture with no reaction, but this suture was not exposed to the inflammatory response of the body and hence has no value in illustrating the body's response to foreign material. In fact, multifilament sutures can cause a florid foreign body giant cell reaction and the so-called suture granulomas.

Figure set 20 (20a-20b)

Dystrophic calcifications occur post-injury (surgical) and direct causation by the mesh cannot be established just by their presence in histologic sections.